



QUESTIONS AND ANSWERS ABOUT . . .

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## **The Use of Hormones After Menopause for Osteoporosis and Recent Findings from the Women’s Health Initiative**

### **What is the Women’s Health Initiative?**

The Women’s Health Initiative (WHI) is a long-term study of the risks and benefits of strategies that may reduce the occurrence of heart disease, breast and colorectal cancer, and bone fractures in postmenopausal women. More than 160,000 healthy postmenopausal women aged 50 to 79 were enrolled as WHI participants between 1993 and 1998. One part of the WHI is a clinical trial designed to study the long-term effects of postmenopausal hormone therapy on heart disease, osteoporosis, and colorectal and breast cancer risk. The hormone trial has two parts: one part has been looking at the effects of estrogen plus a progestin (a form of the hormone progesterone) in 16,608 postmenopausal women who have a uterus (that is, women who have not had a hysterectomy); the other part is looking at the effects of estrogen alone in 10,739 women who have had a hysterectomy. For women with an intact uterus, a progestin is given together with estrogen because estrogen alone has been shown to increase the risk of endometrial cancer (cancer of the lining of the uterus).

In each part of the hormone trial, half of the women were randomly chosen to receive hormone pills, and the other half to receive placebo pills (inactive pills). Neither the study participants nor the researchers know who is taking hormones and who is taking a placebo. Medical studies with this design, known as randomized, controlled, double-blind clinical trials, are considered the “gold standard” for demonstrating a cause-and-effect connection between a particular treatment or behavior and a medical condition or result because they provide the most scientifically reliable information.

## **Why were the women in the WHI estrogen plus progestin clinical trial told to stop taking the study medication in July 2002?**

An analysis by members of the independent Data Safety and Monitoring Board (DSMB) that monitors the health of participants during the study found that women taking the estrogen plus progestin combination had an increased risk of breast cancer compared to women taking placebo pills. The DSMB analysis also indicated that the overall health risks of taking estrogen plus progestin outweighed the benefits. In addition to an increased breast cancer risk, women in the estrogen plus progestin group had an increased risk of heart attacks, strokes, and blood clots in the lungs and legs.

## **What are the effects of estrogen and menopause on bone health in women?**

Estrogen is a hormone produced by the ovaries and in small quantities by other body tissues. Estrogen plays a critical role in building and maintaining bone in adolescent and younger women. Throughout a person's lifetime, old bone is removed and new bone is added to the skeleton. In childhood and adolescence, new bone is added faster than old bone is removed, and the bones become larger, heavier, and denser. Women usually reach their maximum amount of bone, known as peak bone mass, between the ages of 20 and 30. After that, bone mass may remain stable or decline gradually, depending on a variety of lifestyle factors. Calcium and vitamin D and physical activity are also important for building bone and maintaining bone throughout life.

The reduction in estrogen production during menopause is the major cause of bone loss in women during later life. In the few years before menopause (defined as the completion of a full year without a menstrual period), the amount of estrogen produced by the ovaries starts to drop, resulting in a loss of bone mass. During menopause, the rate of bone loss increases as the amount of estrogen produced by the ovaries drops dramatically. Estrogen levels in postmenopausal women are about one-tenth the levels in pre-menopausal women. Bone loss is most rapid in the first few years after menopause but continues into the postmenopausal years.

Loss of bone mass due to low estrogen levels can also occur after a woman has had surgery to remove both her ovaries. This is sometimes called "surgical menopause." Surgical menopause can also result from failure of the ovaries following a hysterectomy, or following cancer therapy, such as chemotherapy or radiation treatments. Bone loss due to either natural or surgical menopause can lead to osteoporosis. But bone loss after menopause and with aging is natural and tolerable in many women and does not need to be treated unless the bone loss is so great that it leaves the bones fragile and prone to fracture.

## **What is osteoporosis?**

Osteoporosis is a skeletal disorder marked by reduced bone strength that predisposes a person to an increased risk of fractures. Bone strength reflects two main features: bone density (which is related to bone mass) and bone quality.

## **What causes osteoporosis?**

Three main factors cause osteoporosis: (1) an increased rate of bone loss at menopause in women or as men and women age; (2) less than optimal bone growth during childhood and adolescence, resulting in failure to reach optimal peak bone mass; and (3) bone loss that is secondary to disease conditions, eating disorders, or certain medications and medical treatments. More than one factor may contribute to osteoporosis. For example, if a woman starts out with a relatively low peak bone mass, the loss of bone that occurs with menopause is more likely to result in osteoporosis.

## **What is known about the effects of postmenopausal hormone therapy on bone health?**

Studies have shown that various forms of estrogen, including estrogen combined with progestin, can increase bone density or prevent bone loss in postmenopausal women. Results of some small clinical trials also indicated that estrogen reduces fractures in the spine. However, there were no large randomized clinical trials showing that estrogen prevents hip and other osteoporosis-related fractures. Research also indicates that women who take estrogen to maintain bone density must continue taking the hormone because its beneficial effects on bone health disappear after hormone use is discontinued.

## **Did the WHI clinical trial of postmenopausal hormone therapy reveal any new information on the effects of estrogen plus progestin on bone health?**

Yes. The WHI is the first randomized clinical trial to provide definitive evidence that postmenopausal hormone therapy can prevent osteoporosis-related hip fractures as well as fractures at other sites. The WHI results show that estrogen plus progestin reduces the rate of hip and spine fractures by one third (34 percent) and reduces the rate of other osteoporosis-related fractures by 23 percent. Stated another way, the study results indicate that for every 10,000 postmenopausal women taking estrogen plus progestin, 10 will have a hip fracture each year, compared to 15 out of every 10,000 women taking placebo pills.

## **What do the WHI results tell us about the effects of estrogen alone on bone health and other conditions?**

The second part of the WHI hormone therapy trial is looking at the effects of estrogen alone on osteoporosis, heart disease, and breast and colorectal cancer in women who have had a hysterectomy. This part of the study is continuing, and results are not yet available. Members of the WHI data safety and monitoring board who reviewed the estrogen-progestin trial results are also regularly reviewing the results of the estrogen study to monitor the potential health risks of the study medication.

## **Do you have any information or recommendations about other hormone therapies for osteoporosis, such as lower-dose estrogens, estrogen patches, or natural estrogens such as phytoestrogens (plant estrogens)?**

The effects of phytoestrogens on bone are still under investigation. However, research indicates that other estrogen preparations are likely to be effective for reducing bone loss that contributes to osteoporosis. For example, a small clinical trial supported by NIAMS showed that daily low-dose estrogen plus progestin, together with adequate calcium and vitamin D intake, reduced bone loss in women over age 65. Women in this study took 0.3 milligrams of estrogen daily, which is slightly less than half of the amount of estrogen used in the WHI hormone trial (0.625 milligrams). We cannot make recommendations about specific hormone therapies for osteoporosis. We recommend that you talk to your doctor or other health care provider about your individual health risk profile and the potential risks and benefits of various treatment options.

## **My doctor tells me that I have osteoporosis and that I am at high risk of fractures, but she advises me that estrogen is not right for me because of my other health conditions and concerns. Are there other medications I can take to prevent fractures?**

The U.S. Food and Drug Administration (FDA) has approved several other medications for prevention and/or treatment of osteoporosis, based on the ability to reduce fractures. These medications are listed below.

- Alendronate (brand name: Fosamax®) is approved for the prevention and treatment of osteoporosis. Alendronate is one of a group of drugs known as bisphosphonates, which reduce the activity of cells that cause bone loss. In postmenopausal women with osteoporosis, alendronate reduces bone loss, increases bone density in both the

spine and hip, and reduces the risk of spine fractures and hip fractures. Alendronate is taken as a daily or once-a-week pill. Possible side effects include abdominal discomfort; muscle, bone, or joint soreness or aches; stomach upset, nausea, vomiting, diarrhea, or constipation; irritation or pain of the esophagus; eye pain; a rash; or an altered sense of taste. Stomach ulcers, although rare, may also occur with alendronate.

- Risedronate (Actonel®) is another bisphosphonate approved for the prevention and treatment of osteoporosis. It increases bone density, reduces the risk of spine fractures, and reduces the risk of non-spinal fractures in women with osteoporosis. Risedronate has been shown to slow or stop bone loss, increase bone mineral density, and reduce the risk of spine and non-spine fractures. Risedronate is taken as a daily or once-a-week pill. Possible side effects include abdominal discomfort; stomach upset, vomiting, nausea, or diarrhea; headache; and muscle or joint soreness or aches.
- Raloxifene (Evista®) is approved for the treatment and prevention of osteoporosis. It is one of a relatively new group of drugs known as selective estrogen receptor modulators, or SERMs. These drugs are not estrogens, but they have estrogen-like effects on some tissues and anti-estrogen effects on other tissues. Raloxifene mimics the effects of estrogen on bones, but does not have estrogen's effects on breast tissue or the uterus. Raloxifene has been shown to prevent bone loss, have beneficial effects on bone mass, and reduce the risk of spine fractures. It is taken as a tablet once a day. Side effects may include hot flashes, sweating, clot formation in some blood vessels, muscle soreness, weight gain, or a rash.
- Calcitonin (Miacalcin®, Calcimar®) is approved for the treatment of osteoporosis in women who are at least 5 years beyond menopause. Calcitonin is a hormone involved in calcium regulation and bone metabolism. It is taken as a single daily nasal spray or as an injection under the skin. In women who are at least 5 years beyond menopause, calcitonin slows bone loss and increases spinal bone density. Some patients report that calcitonin also relieves pain from bone fractures. The effects of calcitonin on fracture risk are still unclear. Injected calcitonin does not affect other organs or systems in the body besides bone, but it may cause an allergic reaction. Side effects may include flushing of the face and hands, increased urinary frequency, nausea, and skin rash. The only side effects reported with nasal calcitonin are a runny nose and other signs of nasal irritation.

## **Are there any other steps I can take to prevent osteoporosis and fractures or keep osteoporosis from worsening?**

Yes, there are many things you can do. Eat a healthy, balanced diet that is high in fruits and vegetables and includes adequate calcium, vitamin D, and vitamin K. Dietary sources of calcium and vitamins are best, but they are also available as supplements. You should also avoid smoking and, if you drink alcohol, do so in moderation. Exercise can also help maintain bone health. Regular, weight-bearing exercise (for example, walking, hiking, jogging, stair-climbing, weight training, tennis, and dancing) may strengthen bone, and balancing and muscle-strengthening exercises can reduce your risk of falling and therefore lessen your chances of breaking a bone.

To reduce your risk of fracture, it's also important to take steps to eliminate factors in your environment that can lead to falls. Some of the many things you can do to avoid falls indoors include keeping rooms free of clutter, keeping floors smooth but not slippery, checking that all carpets and area rugs have skid-proof backing or are tacked to the floor, installing grab bars and using a rubber bath mat in your tub or shower, avoiding obstacles that you might trip over, having your vision checked regularly, and using a nightlight or flashlight if you get up at night. To avoid falls outdoors, use a cane or walker if you need it for added stability, wear rubber-soled shoes for traction, walk on grass when sidewalks are slippery, and sprinkle salt or kitty litter on slippery sidewalks in winter.

## **I have arthritis and I have been told that I might be at risk for osteoporosis because of some of the medications that I have taken. Is there anything special I can do to prevent osteoporosis?**

Stay as active as possible and eat a healthy diet that includes adequate calcium and vitamins, as suggested above. In addition, the medications approved by the FDA for osteoporosis are fine for you to take too. Talk to your health care provider and consult the organizations listed below for more information about specific medications that you can take to prevent osteoporosis.

## **Is the WHI study looking at any other ways to prevent or treat osteoporosis?**

Yes. Another part of the WHI is a randomized controlled clinical trial of calcium and vitamin D supplements in almost 37,000 postmenopausal women. This clinical trial is testing whether taking 1,000 milligrams of calcium carbonate plus 400 IU (International Units) of vitamin D daily can prevent hip fractures and other osteoporosis-related fractures and reduce the risk of colorectal cancer. Results of this study will be available in 2005.

## **Are any other treatments for osteoporosis in development?**

Yes. A new medication, parathyroid hormone (PTH), is pending approval by the FDA for treatment of osteoporosis. Unlike other osteoporosis drugs, which prevent or reduce bone loss, PTH has been shown to stimulate new bone formation. PTH is taken by injection. Researchers are studying other bisphosphonates and SERMs, and looking at the effectiveness of combination therapies for osteoporosis. They are also investigating new approaches for preventing and treating osteoporosis, including the role of statin (cholesterol-lowering) drugs, phytoestrogens (plant estrogens), nitric oxide (a medication often given to heart patients in the form of nitroglycerin), biophysical (vibrational) stimulation of bone, and gene therapy.

## **Where can I get more information about osteoporosis, including its diagnosis, prevention, and treatment?**

For more information on osteoporosis, contact:

- NIH Osteoporosis and Related Bone Diseases-National Resource Center  
2 AMS Circle  
Bethesda, MD 20892-3676  
Phone: (202) 223-0344 or (800) 624-BONE (2663) (free of charge)  
TTY: (202) 466-4215  
Fax: (202) 293-2356  
[www.niams.nih.gov/bone](http://www.niams.nih.gov/bone)
  
- National Osteoporosis Foundation  
1232 22nd Street NW  
Washington, DC 20037-1292  
Phone: (202) 223-2226  
Fax: (202) 223-2237  
[www.nof.org](http://www.nof.org)

For general information on NIAMS and its research programs, contact:

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